Pharmacy Update
September/October 2002
SPECIAL ISSUE

Drug Information Service
Department of Pharmacy
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

Management of Protease Inhibitor-Associated Hyperlipidemia

Scott R. Penzak, Pharm.D.[1], Susan K. Chuck, Pharm.D.[2]
[1]*Pharmacokineticist, Clinical Pharmacokinetics Laboratory National Institutes of Health, Bethesda, MD*
[2]*Clinical Pharmacist Specialist, Anti-infectives, Department of Pharmacy and Drug Information, Grady Health System, Atlanta, GA*

Disturbances in lipid metabolism have been recognized among patients with human immunodeficiency virus (HIV) infection for over a decade.[1] Progression of HIV disease is associated with elevated triglyceride levels and reduced total, HDL, and LDL cholesterol.[1,2] Dyslipidemia secondary to HIV infection is postulated to relate to elevations in circulating cytokines that modulate lipid metabolism.[3-5] Systemic concentrations of Interferon-α correlate with impaired triglyceride clearance and increased *de novo* lipogenesis in patients with HIV infection.[4,5] Prior to the availability of HIV protease inhibitors, zidovudine monotherapy resulted in a 61 mg/dL (0.69 mmol) decline in triglyceride levels and a 78% reduction in interferon-a levels in ten HIV-infected patients treated for 4 months.[6] These data support a relationship between interferon-α and hypertriglyceridemia in patients with HIV infection; the precise nature of this relationship is uncertain. Likewise, the acute phase reactant, tumor necrosis factor-α (TNF-α), which rises during opportunistic infections, has been associated with reductions in total cholesterol in patients with HIV infection.[7] Thus, elevations in interferon-α and TNF-α that occur secondary to HIV and opportunistic infections, appear to be related to altered lipid metabolism in HIV infected patients. Further study is necessary to characterize this relationship.

Hyperlipidemia with HIV Protease Inhibitor Use

Background

In addition to the effects of HIV, alterations in cholesterol and triglyceride levels have also been observed with the use of HIV-1 protease inhibitors.[8,9] HIV-1 protease inhibitors increase survival and improve quality of life in patients with HIV infection.[10] Nonetheless, their ability to raise serum lipid concentrations in patients with HIV infection is now well-described. Increased cholesterol and triglycerides were first reported with the HIV protease inhibitor ritonavir in a 1995 study in HIV-infected patients.[11] After one week of therapy, increases of 30 to 40% and 200 to 300% were observed in total cholesterol and triglycerides, respectively. Since 1997, countless additional studies have documented elevated total cholesterol and triglyceride concentrations in HIV-infected protease inhibitor recipients.[8] Frequently, studies have reported protease inhibitor-related hyperlipidemia in the context of a syndrome of abnormal fat redistribution marked by peripheral fat wasting, central adiposity, and insulin resistance — although any of these conditions may occur independently of the others.[12]

Prevalence

The prevalence of hyperlipidemia in patients receiving HIV protease inhibitors is difficult to assess since it is often reported as part of a metabolic syndrome, for which there is not a specific case definition. Nonetheless, in a well-designed study among a cohort of 454 patients, Romeu and coworkers observed that 26 and 31% of study subjects experienced abnormal elevations in total cholesterol (> 200 mg/dL [5.2 mmol/L]) and triglycerides (> 177 mg/dL [2 mmol/L]) respectively, after one year of protease inhibitor therapy.[13] After two and three years of treatment with protease inhibitors, 51 and 60%, and 83 and 78% of patients experienced elevations in cholesterol and triglycerides, respectively. These data suggest that hypercholesterolemia and hypertriglyceridemia occur in greater than 50% of protease inhibitor recipients after 2 years and that the risk of developing hyperlipidemia increases with duration of protease inhibitor therapy.

Characterization of Lipoprotein Abnormalities

Initial investigations of hyperlipidemia with protease inhibitor use typically reported elevations in total cholesterol and triglyceride concentrations; LDL and HDL cholesterol were infrequently addressed.[8] This is because a substantial number of patients in these studies had triglyceride concentrations > 400 mg/dL (4.5 mmol/L), thereby preventing the accurate calculation of LDL cholesterol. More recently, investigations have addressed these lipid subfractions.[14-16] Typically, the lipid profile of HIV-infected patients receiving protease inhibitors is characterized by the combined effects of the patient's underlying disease (HIV) and antiretroviral pharmacotherapy (protease inhibitors). Total cholesterol, triglycerides, and LDL cholesterol are usually elevated while HDL is often reduced.[1,8] In 256 HIV-infected patients receiving protease inhibitor-containing highly active antiretroviral therapy (HAART), 27% were noted to have total cholesterol levels > 251 mg/dL (6.5 mmol/L) compared to 3% of 84 treatment-naïve HIV-positive patients ($P < .0001$).[16] Similarly, 56% of HAART recipients had triglyceride levels > 150 mg/dL (1.7 mmol/L) compared to 31% of protease inhibitor-naïve patients ($P < .0001$); 33% of HAART recipients had LDL levels > 160 mg/dL (4.14 mmol/L) compared to 5% of treatment-naïve patients ($P < .0001$).[16] HDL cholesterol was below 35 mg/dL (0.9 mmol/L) in 27% of patients on HAART compared to 31% of treatment naïve patients (P = not significant), suggesting that protease inhibitor therapy is not associated with further reductions in HDL cholesterol beyond those observed with HIV infection itself.

In addition to lipoprotein abnormalities described above, several studies have also reported an increase in Lp(a) levels among patients on HAART.[16,17] Lp(a) is a carrier protein for LDL which is structurally similar to LDL and plasminogen.[18] Increased levels of Lp(a) impair fibrinolytic activity and pose an independent risk for coronary heart disease (CHD).[19] Koppel and co-workers reported that very high Lp(a) levels (> 700 mg/dL) were more common among patients on HAART > 2 years compared with antiretroviral naïve patients (14 versus 2%, respectively; $P = .0022$).[16] Périard et al. reported similar elevations in Lp(a) in patients who started HAART with baseline Lp(a) values > 200 mg/dL.[17] Moreover, patients with AIDS also have a greater prevalence of LDL-B — a phenotype primarily comprised of smaller and denser LDL particles.[4,20] Whether alterations in these lipoproteins are associated with further risk of atherosclerotic disease in patients with HIV infection and/or those receiving protease inhibitors is unclear at this time.

The degree to which triglycerides, and total and LDL cholesterol are elevated with protease inhibitor therapy varies among published data.[8] In a recent review, the median increase in total cholesterol and triglycerides among 30 investigations of protease inhibitor-associated hyperlipidemia, was 29% and 105%, respectively.[8] However, reports of marked increases in total cholesterol (> 400 mg/dL [10.4 mmol/L) and triglycerides (> 1000-2000 mg/dL [11.3 – 22.6 mmol/L) are not uncommon with protease inhibitor use .[8,21] In one report, a 35 year-old man was noted to have a total cholesterol of 967 mg/dL (25 mmol/L) and triglycerides of 5465 mg/dL (61.8 mmol/L) after 4 months on ritonavir.[21]

Although all available HIV protease inhibitors have been associated with hyperlipidemia, data generally show a higher prevalence with ritonavir.[8,12,13] In a group of healthy volunteers, total cholesterol increased by 24% and triglycerides by 137% within 2 weeks of starting the drug.[22] Similarly, significant increases in total cholesterol and triglycerides were observed among patients with HIV infection after 1 week of ritonavir therapy.[11] Even when used in low doses (400-800 mg/day) as a pharmacokinetic enhancer (to boost plasma concentrations of concurrently administered protease inhibitors) ritonavir was still associated with elevations in total cholesterol (> 200 mg/dL [5.2 mmol/L]) and triglycerides (> 200 mg/dL [2.3 mmol/L]) in greater than 61% of 94 HIV-infected patients.[23] The combination product lopinavir-ritonavir, administered as 400 mg lopinavir plus 100 mg ritonavir twice daily, was associated with marked elevations in cholesterol (> 300 mg/dL) and triglycerides (> 750 mg/dL) in 6.7 % and 5.1% of 326 (previously) antiretroviral naive patients.[24] In 186 antiretroviral experienced patients who received lopinavir (400-533 mg) plus ritonavir (100-200 mg) twice daily in combination with NRTIs and NNRTIs (efavirenz or nevirapine), elevations in cholesterol (> 300 mg/dL) and triglycerides (> 750 mg/dL) were even greater at 25.7 and 26.2%, respectively.[24]

Proposed Mechanisms

The exact mechanism by which HIV protease inhibitors induce hyperlipidemia is unclear. Two human proteins involved in lipid metabolism, Cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low density lipoprotein-receptor related protein (LRP), are similar in amino acid sequence to the catalytic region of HIV-1 protease.[25] This similarity led Carr and coworkers

to hypothesize that HIV protease inhibitors bind to CRABP-1 thereby interfering with a series of biological steps involved in normal lipid regulation.[25] These investigators also hypothesized that CYP3A inhibition by HIV protease inhibitors may contribute to abnormal lipid regulation. However, these hypotheses have not been uniformly supported when tested in a series of preclinical investigations.[26-29]

Recent data suggest that hyperlipidemia associated with protease inhibitor use may result from increased production of VLDL particles by the liver.[28,30] This accelerated production of triglyceride-rich lipoproteins appears to be due to activation of lipogenic genes in the liver, which are controlled by sterol regulatory element-binding protein (SREBP-1c). Interestingly, SREBP-1c was found to be increased in the nucleus of liver cells of ritonavir-treated mice.[31] Additionally, SREBP is transactivated in animals by insulin, and hyperinsulinemia — with insulin resistance — is common among protease inhibitor recipients with lipodystrophy.[30,32] As such, chronically elevated insulin levels in these patients may lead to continuous activation of SREBPs resulting in hyperlipidemia.

In summary, several theories have been proposed to explain how protease inhibitors interfere with lipid metabolism, but the mechanism by which this occurs remains largely unknown. In all probability, multiple metabolic pathways that regulate lipid storage and metabolism are modulated directly and indirectly by HIV protease inhibitors. Nutritional status and genetic predisposition may also predispose certain patients to protease inhibitor-associated hyperlipidemia.[30] It is clear that continued study is necessary to elucidate the precise mechanisms by which protease inhibitors alter lipid metabolism.

Pathogenic Complications Potentially Associated with Protease Inhibitor use

Atherosclerotic Disease

Cardiovascular complications, including atherosclerotic disease, occur with increased frequency in patients with HIV infection.[33] The mechanisms by which HIV infection appears to accelerate atherosclerosis are multifactorial and the subject of two recent reviews.[33,34] Briefly, these mechanisms include direct endothelial dysfunction resulting in vasculitis and arteriosclerosis, oxidative stress secondary to cytokine-induced disruption of the endothelial nitric oxide synthase (eNOS) system, and activation of endothelial cells and expression of adhesion molecules due to the HIV regulatory protein *Tat*.[33,34] Metabolic perturbations, including changes in body composition, insulin resistance, low HDL, and elevated triglycerides may also contribute to premature atherosclerosis in patients with HIV infection.[34]

In addition to HIV infection, antiretroviral medications may also have deleterious cardiovascular effects. Nucleoside analogue reverse transcriptase inhibitors (NRTI) potentially contribute to premature atherosclerosis and end-organ damage by disrupting mitochondrial function in the arterial system.[34] Nonetheless, anecdotal reports of atherosclerotic cardiovascular disease have been reported most frequently with HIV protease inhibitor use (Table 1).[35-39] In these cases, most patients presented with myocardial infarction or angina, had elevated total cholesterol and triglyceride levels (mean total cholesterol and triglyceride concentrations among 9 patients were 337 mg/dL (172-630 mg/dL) [8.7 mmol/L; 4.5-16.3 mmol/L] and 644 mg/dL (111-1959 mg/dL) [7.3 mmol/L; 1.3-22.1 mmol/L], respectively), and had been receiving protease inhibitor-containing HAART for an average of 10 months. Moreover, in addition to hyperlipidemia, many patients were noted to possess additional risk factors for the development of CHD; most frequently, these included cigarette smoking and being a male over (or equal to) 45 years of age. The majority of patients were successfully treated with percutaneous transluminal coronary angioplasty (PCTA), beta-blockers, aspirin, and dietary modification. Of note, because coronary events were observed in most of these patient shortly after protease inhibitor initiation, it has been postulated that they may have occurred secondary to an immune reconstitution disease such as cytomegalovirus or *Chlamydia pneumoniae*.

In response to anecdotal reports of CHD associated with protease inhibitor use, several studies have attempted to characterize the risk of CHD in protease recipients in a controlled fashion.[40-44] Klein et al. noted a higher rate of CHD events among 4,541 patients with HIV infection (5.5 CHD [CI: 3.8-7.3] per 1000 patient-years) compared to non-HIV infected controls (2.8 CHD events [CI: 2.5-3.1] per 1000 patient-years); however there was no difference in the rate of CHD events among HIV infected patients who received protease inhibitors compared to those who did not (5.8 [CI: 3.4-8.2] and 5.2 [CI: 2.7-7.7], respectively).[40] These observations are consistent with recent data from the MediCal data base, which showed increased CHD in HIV-infected men between 18 to 34 years of age compared to non HIV-infected men of the same age.[44] Most of the HIV-infected men who developed CHD in this study, did so within 2 years of initiating antiretroviral therapy.[44]

Coplan and coworkers conducted a retrospective investigation in 2,680 HIV-infected patients receiving indinavir or NRTI therapy, or both to determine the comparative risk of myocardial infarction, angina, unexpected death, stroke and peripheral vascular disease.[41] Relative risk of CHD was not increased among indinavir recipients relative to control patients receiving NRTI therapy only (RR: 0.96). Nonetheless, confidence intervals were wide (0.31-3.50) and duration of follow-up was short (one year). Of interest, the investigators did note a statistically significant increase in the risk of myocardial infarction among indinavir recipients with CD4+ counts < 50 cells/mm^3 compared to those with counts between 50 and 500 cells/mm^3. The incidence of myocardial infarction was 6.97 per 1000 person-years among 324 patients with CD4+ cells ≤ 50 compared with 1.22 per 1000 person-years for the 1753 patients with CD4+ cell counts between 50 and 500 cells/mm^3 ($P = .048$).

Conversely, Jütte and colleagues observed a trend toward a higher incidence of myocardial infarction in 373 protease inhibitor recipients (1.3%) compared to 951 patients not receiving the drugs (0.3%; $P = .08$).[42] All five patients on protease inhibitor therapy who experienced myocardial infarction were male, a median of 50 years old, had no previous history of CHD, and had at least two coronary risk factors; four of these patients had severe hypercholesterolemia.

Mary-Krause and colleagues observed a higher incidence of myocardial infarction in HIV-infected patients receiving protease inhibitors > 18 months compared to that expected for the general non-HIV infected population.[44] Patients exposed to protease inhibitors for 18 to 29 months had an incidence of myocardial infarction of 19.2 ± 4.5 per 10,000 patient-years compared to the expected incidence of 10.8 cases per 10,000 patient-years in members of the general population of the same sex and age. However, this study did not include a control group of HIV infected recipients not on protease inhibitors for comparison; thus the influence of HIV infection versus protease inhibitor exposure cannot be distinguished with regard to their contribution to myocardial infarction.

Despite compelling anecdotal evidence that protease inhibitor therapy may result in premature CHD, controlled — albeit preliminary — data suggest that such cases are uncommon.[40-42] Nonetheless, caution must be exercised when attempting to draw conclusions from large data bases that do not control for concurrent CHD risks such as smoking, age etc. Further, use of recreational drugs among HIV infected patients may contribute to CHD and must also be considered. Degree of immunosuppression, baseline lipid levels and duration of protease inhibitor use may also contribute to accelerated CHD.[35-39,41,44] Studies with large numbers of patients (tens of thousands) followed over many years (> 5-10 years) will be necessary to determine the risk, if any, of CHD with protease inhibitor use.

Table 1. Case Reports of Vascular Complications in Patients Receiving Protease Inhibitors

CHD Event[a]	Age	Sex	Involved Protease inhibitor(s) (Duration)	Concomitant CHD Risks	Serum Lipid Concentrations at /prior to CHD Event[b]	Treatment[c]	Reference
angina pectoris	60	male	saquinavir(9 months)	age/sex; smoking	CH: 282 mg/dL LDL: 201 mg/dL	not reported	35
embolic occlusion of femoral artery; atherosclerotic plaques in carotid arteries	58	male	indinavir + "others" (19 months)	age/sex	CH: 282 mg/dL LDL: 178 mg/dL HDL: 35 mg/dL TG: 274 mg/dL	lysis and dilatation	35
inferior posterior wall MI (x 2)	33	male	ritonavir (14 months)	smoking	CH: 220 mg/dL TG: 260 mg/dL	PTCA (x 2)	36
anterolateral wall MI	32	male	indinavir (18 months)	smoking	CH: 172 mg/dL TG: 111 mg/dL	PTCA	36
angina; ST segment depression	54	male	saquinavir (9 months)	age/sex	CH: 630 mg/dL TG: 861 mg/dL	fenofibrate; acebutolol; nitroglycerin patch; aspirin	36
anteroseptal MI	36	not reported	indinavir (12 months)	smoking; hypertension	TG: 363 mg/dL	PTCA	37
TIAs	40	not reported	indinavir (16 months)	smoking	CH: 278 mg/dL TG: 699 mg/dL	b-blockers; aspirin; dietary modification	37
anteroseptal MI	47	not reported	indinavir (0.75 month)	"genetic factors"	CH: 293 mg/dL	PTCA; b-blockers; aspirin; dietary modification	37
acute infero-posterior MI	41	male	ritonavir (15 months)	smoking	CH: 398 mg/dL TG: 630 mg/dL	PTCA; fluvastatin	38
RCA thrombus + angina	26	male	ritonavir + Saquinavir (1 month)	cigarettes; prior cocaine abuse	not reported	not reported	39
LAD occlusion + RCA atherosclerosis + angina	37	male	indinavir (1 month)	diabetes mellitus; family history; smoking	CH: 475 mg/dL HDL: 18 mg/dL TG: 1959 mg/dL	gemfibrozil; aspirin	39

[a] MI: Myocardial infarction; RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; TIAL Transient Ischemic Attack

[b] CH: Total Cholesterol; LDL: Low-density lipoprotein; HDL: High density lipoprotein; TG: Triglycerides
To convert mg/dL to mmol/L: multiply by 0.02586 for cholesterol and by 0.0129 for triglycerides

[c] PTCA: Primary Percutaneous Transluminal Coronary Angioplasty

In lieu of definitive epidemiological data, coronary artery calcium and carotid media intima thickness have been assessed as markers for atherosclerosis among protease inhibitor recipients.[45-48] Maggi and coworkers found that 29/55 (53%) of protease inhibitor-treated patients had premature carotid lesions via ultrasonography compared to 7/47 (15%) of protease inhibitor-naïve patients ($P = .011$).[49] In addition to protease inhibitor use, age, male sex, hypercholesterolemia, cigarette smoking, hypertriglyceridemia, and Center for Disease Control and Prevention stage were significantly associated with vascular lesions. Depairon et al. used ultrasonography to assess the carotid and femoral arteries of 131 HIV-infected protease inhibitor recipients (mean duration: 27 months).[50] Despite the frequent detection of carotid and femoral plaques, multivariate logistic regression analysis identified cigarette smoking and age as significant risk factors for plaque formation; protease inhibitor use was not found to be a risk.

Carotid intima media thickness was assessed in 29 HIV infected patients on protease inhibitors with cholesterol > 259 mg/dL (6.7 mmol/L) and/or triglycerides > 310 mg/dL (3.5 mmol/L).[45] An increased carotid intima media thickness was observed in 10/29 (35%) of patients. Age and LDL cholesterol were significantly related to increases in carotid media thickness ($P = .0035$ and $P = .016$, respectively) while duration of protease inhibitor therapy was not. However, protease inhibitor duration was relatively consistent among patients (30.6 ± 10 months), thus it is likely that the study was not powered to detect differences in carotid intima media thickness based on protease inhibitor duration.

At least 3 investigations have used electron-beam computed tomography (EBCT) to assess coronary artery calcium — an established marker of subclinical CHD — in protease inhibitor recipients.[46-48] In the first study, 5/17 HIV-positive patients receiving protease inhibitors for > 1 year, had elevated coronary artery calcium (CAC) scores.[46] The mean age of subjects was 46 years (34-56) and they were on protease inhibitor therapy for a mean of 25 months. Four of the patients were male and at least one subject smoked. Three patients had total cholesterol levels > 200 mg/dL (5.2 mmol/L) (214-273 mg/dL [5.5 – 7.1 mmol/L]), and three suffered from hypertension. A second study in nine patients with HIV infection did not find a relationship between protease inhibitor use and elevated CACS; this was probably due to a lack of statistical power.[47] Talwani et al. found no differences in clinically relevant CAC elevations among 60 HIV-infected protease inhibitor naïve patients, 180 HIV-negative controls, and 41 HIV-infected patients on protease inhibitors.[48]

Stein et al. assessed endothelial dysfunction via flow-mediated vasodilation (FMD) of the brachial artery — a predictor of future cardiovascular events — in 37 HIV infected adults; 22 who were taking protease inhibitors and 15 who were not.[51] Lipids and lipoproteins were also measured in these individuals. Protease inhibitor recipients were noted to have impaired FMD (2.6 ± 4.6%) while patients not taking protease inhibitors had normal FMD (8.1 ± 6.7%) ($P = .005$). Among patients receiving protease inhibitors, atherogenic lipoprotein changes (elevations in triglyceride-rich lipoproteins and their cholesterol-rich remnants) predicted FMD.

Similar to epidemiologic data describing CHD among protease inhibitor recipients, studies examining markers of atherosclerotic disease in arterial vessels (CACS and carotid intima thickness) are preliminary in nature, often underpowered, and largely inconclusive. Nonetheless, these data do suggest that male sex, age, cigarette smoking, and hypertension contribute to premature atherosclerosis among protease inhibitor recipients. This is in agreement with anecdotal reports of premature CHD discussed earlier (Table 1).

Pancreatitis

Extremely high triglyceride concentrations (> 1000 mg/dL [>11.3 mmol/L]), which have been reported with protease inhibitor use, are a risk factor for the development of pancreatitis.[8,48] Nelson and coworkers reported a fatal case of pancreatitis in a patient 3 weeks after beginning antiretroviral therapy containing ritonavir, saquinavir, and didanosine; the patient had triglyceride concentrations > 40 times the upper limit of normal.[52-54] Other investigators have also noted cases of pancreatitis in hypertriglyceridemic protease inhibitor recipients.[55,56] Whether didanosine, zalcitabine, and stavudine (NRTIs which may predispose patients to pancreatitis via mitochondrial toxicity) contribute to the risk of pancreatitis in protease inhibitor recipients with hypertriglyceridemia is unknown.

Management

Lipoprotein Assessment

The Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group recently published preliminary guidelines for the treatment of hyperlipidemia in patients with HIV infection receiving HAART.[57] Foremost, the group recommends the use of the National Cholesterol Education Program (NCEP) guidelines as a "reasonable starting point" to manage these patients.[57,58] NCEP guidelines assign a target LDL goal to individual patients based upon the presence of CHD or CHD risk equivalents, and major CHD risk factors. CHD risk equivalents include other forms of atherosclerotic disease (peripheral arterial disease etc.), diabetes, and multiple risk factors that present a 10-year risk for CHD that exceeds 20%. Major CHD risk factors that modify LDL goals include cigarette smoking, hypertension (blood pressure > 140/90 mm Hg or patient receiving antihypertensive medication), low HDL cholesterol (< 40 mg/dL [1.0 mmol/L]), family history of CHD (CHD in a first degree male or female relative < 55 years or < 65 years, respectively), and age (men

≥ 45 years and women ≥ 55 years). LDL goals are < 100 mg/dL (2.6 mmol/L) in patients with CHD or CHD risk equivalents, < 130 mg/dL (3.4 mmol/L) in patients with ≥ 2 CHD risk factors, and < 160 mg/dL (4.1 mmol/L) in patients with ≤ 2 risk factors; life style modifications (primarily diet and exercise) are recommended for all patients above their respective LDL goals. In general, antihyperlipidemic drug therapy should be considered when LDL cholesterol rises to ≥ 30 mg/dL (0.78 mmol/L) above a patient's LDL goal. The reader is referred to NCEP guidelines for an exhaustive discussion on this topic.[58]

Serum lipid concentrations should be evaluated in all HAART recipients prior to therapy initiation (baseline) and at least every 3-6 months thereafter.[57] All lipid profiles should be obtained in the fasting state to allow for the accurate measurement of triglycerides and calculation of LDL cholesterol. Of note, a substantial proportion of patients will present with triglyceride concentrations > 400 mg/dL (4.5 mmol/L), which will preclude the accurate calculation of LDL cholesterol. Since direct measurement of LDL cholesterol is not available in many clinical laboratories, treatment decisions in these patients are often based on total cholesterol, HDL cholesterol, and triglyceride concentrations.[57] In such patients, dietary, and perhaps pharmacological intervention should be considered when total cholesterol exceeds 240 mg/dL (6.2 mmol/L) and HDL cholesterol is less than 40 mg/dL (1.0 mmol/L).[57] In patients with severe isolated hypertriglyceridemia (> 1,000 mg/dL [11.3 mmol/L]), drug therapy should be initiated in most cases to reduce the immediate risk of pancreatitis. Drug therapy may be considered at lower triglyceride concentrations (~ 500 mg/dL [5.7 mmol/L]) in patients with a previous history of pancreatitis.[57] Patients with modestly elevated triglycerides (200-400 mg/dL [2.3 – 4.5 mmol/L]) are not at risk for pancreatitis *per se*, but should undergo dietary and exercise intervention to reduce risk of CHD.

Treatment

Prior to initiating therapeutic interventions, patients should be assessed for potentially contributing factors to hyperlipidemia which may include excessive alcohol intake, hypothyroidism, renal and liver diseases, and hypogonadism.[57] Patients should also be screened for the use of medications that may modulate lipoprotein concentrations; these include β-blockers, thiazide diuretics, thyroid hormones, and other hormones such as androgens and estrogens. Lastly, toxicities and drug interactions with individual antihyperlipidemic agents must be carefully considered and assessed with regard to the patient's clinical condition when initiating therapy.

Lifestyle Modifications

Lifestyle modifications including exercise, dietary intervention, and smoking cessation and weight reduction (if applicable) should be implemented in all HIV-infected patients with LDL cholesterol above their NCEP-recommended goal. Indeed, as discussed earlier, data suggest that cigarette smoking and hypertension may hasten the atherosclerotic process in patients with protease inhibitor-related hyperlipidemia. Therefore, these modifiable risk factors should be addressed foremost, and in general, instituted prior to pharmacologic intervention.

Dietary modification may improve the metabolic profiles of HIV-infected patients with fat redistribution secondary to improving insulin resistance.[59] In a recent study, dietary fiber was inversely associated with insulin area under the concentration-time curve (AUC) among 85 HIV infected patients with fat redistribution ($P = .001$); polyunsaturated-to-saturated fat intake was positively associated with insulin AUC ($P = .003$). However, in a regression model, no clinical or dietary variables significantly predicted triglyceride levels in these patients. Of note, dietary requirements in patients with concurrent wasting and hyperlipidemia may be conflicting; it is recommended that wasting be addressed prior to hyperlipidemia in such patients.[57] Furthermore, certain antiretroviral medications used in HIV-infected patients require the consumption of meals high in fat content (i.e., saquinavir hard or soft-gel capsules) to ensure optimal absorption. In such patients, the minimum amount of dietary fat necessary to ensure the systemic availability of antiretroviral medications should be consumed. Consultation with a dietician may prove beneficial in these and similar situations.

Antihyperlipidemic Therapy. Characteristics of currently available antihyperlipidemic medications are listed in Table 2.[60-63] Below, individual drugs are presented along with special considerations that must be taken into account when they are used in patients with HIV infection. In addition, preliminary studies examining the use of these agents for the treatment of protease inhibitor-associated hyperlipidemia are also discussed.

Antihyperlipidemic Therapy: HMG-CoA reductase inhibitors (Statins). The 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) are typically used as first line antihyperlipidemic agents in non-HIV-infected patients since they have proven effective in both primary and secondary prevention of CHD.[64] The two statins used most frequently in patients receiving HAART are pravastatin and atorvastatin. This is largely because pravastatin is not significantly metabolized by cytochrome P450 (CYP) 3A4 — a metabolic pathway inhibited to varying degrees by the HIV protease inhibitors. Therefore, toxicity due to impaired pravastatin metabolism (resulting in elevated plasma concentrations) is not expected with concurrent protease inhibitor use. Indeed, pravastatin concentrations were not significantly increased by the combinations of saquinavir-ritonavir or lopinavir-ritonavir in two separate pharmacokinetic studies conducted in healthy volunteers under steady-state conditions. Lastly, pravastatin did not alter nelfinavir, ritonavir, or saquinavir concentrations among healthy volunteers.[65,66]

Atorvastatin is partially metabolized by CYP3A4 and should be used with caution in protease inhibitor recipients. Although atorvastatin did not alter ritonavir or saquinavir concentrations, in separate pharmacokinetic studies, saquinavir-ritonavir and lopinavir-ritonavir combinations resulted in 4.5 fold and 5.9 fold increases in atorvastatin AUC, respectively.[65,66] Concomitant nelfinavir resulted in a 74% increase in atorvastatin AUC.[67] Therefore, in patients receiving protease inhibitors, starting atorvastatin doses should not exceed 10 mg and upward titration should be implemented with caution. Liver function tests should be performed prior to statin initiation and every 3 to 6 months thereafter. Of note, many HIV-infected patients are also co-infected with hepatitis B or C virus, which may place them at further risk for LFT elevations with statin therapy. Patients should be instructed to report any symptoms of muscle discomfort to their health care provider and symptoms of myalgia should be followed up with plasma creatine kinase determinations.

Simvastatin and lovastatin are significantly metabolized by CYP3A4 and are not recommended for coadministration with protease inhibitors.[68] Simvastatin concentrations rose 31.6 fold when coadministered with a saquinavir-ritonavir combination and 506% when given with nelfinavir in two pharmacokinetic investigations.[65,67] Indeed, severe rhabdomyolysis with acute renal failure was recently reported in a patient receiving simvastatin with concurrent protease inhibitor therapy.[69] In a separate report, myalgia and elevated creatine kinase concentrations were noted with lovastatin in combination with protease inhibitors.[70]

Fluvastatin is primarily metabolized by CYP2C9 and is not expected to interact with HIV protease inhibitors.[8,60] However, because fluvastatin is weaker in reducing LDL cholesterol compared to other statins, its role in treating protease inhibitor-associated hyperlipidemia is undefined. Lastly, cerivastatin has recently been removed from the United States market due to an unacceptably high incidence of skeletal muscle toxicity, including fatal rhabdomyolysis.[71]

Pharmacokinetic interactions between statins and NNRTIs have not been evaluated to date. Nonetheless, nevirapine and delavirdine induce and inhibit CYP3A4, respectively.[68] Therefore, nevirapine and delavirdine may be expected to decrease and increase the systemic exposure of simvastatin, lovastatin, and atorvastatin, respectively. Efavirenz may inhibit or induce CYP3A4 and therefore may variably affect the plasma concentrations of these statins. Pravastatin and fluvastatin are likely to be less-affected by concomitant NNRTI therapy, although pharmacokinetic studies are necessary to confirm or refute this theory.

Antihyperlipidemic Therapy: Fibric acid derivatives. Gemfibrozil and fenofibrate are both effective in significantly lowering triglycerides and raising HDL cholesterol; fenofibrate also tends to lower LDL cholesterol.[61] Bezafibrate, a fibric acid derivative available in Canada and Europe but not the United States, is similarly effective.[61] Clofibrate, on the other hand, is associated with increased mortality secondary to malignant and gastrointestinal disease and should be avoided.[72] All of the fibrates can cause cholelithiasis, hepatitis, and myositis, and patients should be monitored accordingly.[61] Furthermore, fibrates may increase the risk of skeletal muscle toxicity when coadministered

Table 2. Characteristics of Antihyperlipidemic Medications[60-63]

Antihyperlipidemic	Dosage and Administration	Metabolic Route
Statins		
pravastatin (Pravachol™)	20-40 mg at bedtime (without food)	sulfation (not CYP3A4-mediated)
atorvastatin (Lipitor™)	10-80 mg in the evening (± food)	primarily CYP3A4
fluvastatin (Lescol™)	20-40 mg at bedtime (± food)	CYP2C9
simvastatin (Zocor™)	20-80 mg in the evening (± food)	CYP3A4
lovastatin (Mevacor™)	20-80 mg with meals (am and pm)	CYP3A4
Fibric acid derivatives		
gemfibrozil (Lopid™)	600 mg twice daily 30 minutes before am and pm meals	glucuronosyl transferases
fenofibrate (Tricor™)	201 mg once daily	esterases; glucuronosyl transferases
clofibrate (Atromid™	1 gram twice daily	esterification
Niacin Preparations		
niacin immediate release (Niacor™)	1 gram three times daily with meals	glycine conjugation
niacin extended release (Niaspan™)	2 grams once daily	glycine conjugation
Bile-acid binding resins		
cholestyramine (Questran™ and Questran Light™)	8 grams resin per day in divided doses within 1 hr of a meal	not metabolized
colestipol granules and tablets (Colestid™)	10 grams per day in divided doses within 1 hr of a meal	not metabolized

with statins and patients should be closely monitored with regard to myalgias, liver function tests and creatine kinase levels.[8,61]

Gemfibrozil and fenofibrate are not metabolized by cytochrome P450 enzymes, therefore their systemic availability is not expected to rise in the presence of protease inhibitors.[62] However, gemfibrozil is biotransformed by glucuronosyl transferases which are induced by the HIV protease inhibitors nelfinavir and ritonavir.[62,73] Therefore, it is possible that that these protease inhibitors may reduce plasma concentrations of gemfibrozil and compromise the drug's efficacy. One retrospective study noted a decrease in gemfibrozil activity (defined as a rebound increase in triglyceride concentrations) in five patients after the addition of nelfinavir.[74] Fenofibrate is partially biotransformed by glucuronidation and may also interact with nelfinavir and/or ritonavir.[75] These potential pharmacokinetic interactions should be kept in mind when assessing the efficacy of gemfibrozil or fenofibrate in patients receiving nelfinavir or ritonavir-containing HAART regimens.

Antihyperlipidemic Therapy: Niacin. Niacin is effective in lowering triglycerides, and total and LDL cholesterol; it is also effective in raising HDL cholesterol more than any other drug.[61] However, major disadvantages to niacin therapy almost always preclude its use for the treatment of protease inhibitor-associated hyperlipidemia. These include: flushing, pruritis, gastrointestinal distress, fatigue, and hyperuricemia. Furthermore, niacin has been associated with insulin resistance and hepatotoxicity (primarily with older sustained release formulations), both of which can occur with protease inhibitor use.[57,61] Therefore, niacin cannot be routinely recommended for the treatment of protease inhibitor-related hyperlipidemia.

Antihyperlipidemic Therapy: Bile Acid-Binding Resins. Cholestyramine and cholestipol are two bile acid-binding resins that can lower LDL cholesterol up to 20%.[61] However, these drugs are poor choices for the treatment of protease inhibitor-associated hyperlipidemia. First, bile acid binding resins may elevate triglyceride concentrations, which are often already markedly elevated in patients receiving protease inhibitors.[57,61] Second, these agents may interfere with the absorption of concurrently administered medications including anti retrovirals; this may lead to subtherapeutic antiretroviral concentrations, accumulation of resistance mutations, and therapeutic failure.

Antihyperlipidemic Therapy: Fish Oils (omega-3 fatty acid supplements). Fish oils have not been studied for the treatment of hypertriglyceridemia associated with protease inhibitor use although recent guidelines suggest that they may be tried in patients with severe hypertriglyceridemia unresponsive to fibrates.[57] Of note, these agents have been shown to reduce triglyceride levels in patients with AIDS wasting.[76] However, they also possess the potential to actually cause further increases in triglycerides.[57,61] Further study is necessary to define whether fish oils will have a role in treating hypertriglyceridemia in protease inhibitor recipients.

Antihyperlipidemic Therapy: Garlic. Collectively, studies have observed small short-term reductions in total cholesterol, which are paralleled by reductions in LDL cholesterol and triglycerides, with garlic therapy.[77] Compared to placebo, garlic reduced total cholesterol by 12.4-25.4 mg/dL after 3 months of treatment in non-HIV-infected patients.[77] However, no benefit was observed after 6 months. Garlic is currently under study for the treatment of protease inhibitor-associated hyperlipidemia; however, garlic's minimal effects on lipoprotein levels are not likely to be significantly beneficial in protease inhibitor recipients with markedly elevated serum lipids. Furthermore, garlic was recently shown to lower the systemic exposure of saquinavir soft gelatin capsules by 51% in a pharmacokinetic study involving nine healthy volunteers.[78]

Therapeutic Intervention Data

Several small studies have examined pharmacologic and non-pharmacologic management in patients with protease inhibitor-related lipid abnormalities (Table 3).[14,15,70,74,79-85] Henry et al. used NCEP guidelines to treat 74 patients with elevated total cholesterol and/or triglyceride levels.[81] Patient management included diet and exercise (n=20), atorvastatin 10 mg daily to start (n=10), gemfibrozil 600 mg twice daily (n=25), and atorvastatin plus gemfibrozil (n=19). Statistically significant reductions in total cholesterol were observed in all groups, although levels remained above 200 mg/dL (5.2 mmol/L) after 5 to 7 months of treatment. As expected, gemfibrozil, alone and in combination with atorvastatin, resulted in the largest reduction in triglyceride levels, however mean triglyceride concentrations remained above 400 mg/dL (4.5 mmol/L) in both groups. Lowe and coworkers employed NCEP guidelines to assess the effectiveness of pravastatin 20-40 mg daily in treating 17 patients with hyperlipidemia associated with protease inhibitor use.[14] In nine patients with triglycerides < 400 mg/dL, in whom LDL could be calculated, mean LDL cholesterol declined from 216 ± 44 mg/dL to 158 ± 44 mg/dL after 12 weeks of pravastatin treatment ($P = .003$). Triglycerides were lowered 13% with pravastatin (607 ± 625 mg/dL to 526 ± 689 mg/dL; $P = .22$) and HDL cholesterol was not significantly changed.

Collectively, these preliminary data suggest that NCEP guidelines may effectively be used to treat patients with protease inhibitor related hyperlipidemia. Importantly, neither study noted any detrimental effects of statins or fibrates on CD4+ counts or HIV-RNA. As well, no toxicities (myalgia, myopathy, elevated liver function tests or creatine kinase) were associated with statin therapy in either study. Currently, the Adult AIDS Clinical Trials Group (AACTG) is using modified NCEP guidelines to compare fenofibrate 200 mg daily and pravastatin 40 mg daily in a total of 630 HIV-infected HAART recipients. Patients not adequately responding to therapy after 12 weeks of

single-drug therapy will receive fenofibrate and pravastatin in combination. Results from this investigation should yield important information that will help guide antihyperlipidemic therapy among protease inhibitor recipients in the future.

Several additional pilot studies or case series' reported on the efficacy of antihyperlipidemic pharmacotherapy in patients with protease inhibitor-related hyperlipidemia; data from these investigations is outlined in Table 3. Among 72 pravastatin recipients, total cholesterol was reduced 15-21% to a mean concentration of 252 mg/dL (6.5 mmol/L) (247-257 mg/dL [6.4 – 6.7 mmol/L]) after 3 to 9 months follow-up.[14,15,70,79] Atorvastatin reduced total cholesterol 19 to 32% among 25 patients in separate prospective investigations; the mean total cholesterol concentration after 5 to 15 months of follow-up was 234 mg/dL (6.1 mmol/L) (220-247 mg/dL [5.7 – 6.4 mmol/L]).[81,82] Although it is difficult to draw firm conclusions on pooled data from small numbers of patients, pravastatin and atorvastatin appear to be marginally effective in reducing cholesterol in patients with hyperlipidemia associated with protease inhibitor use. However, total cholesterol typically remains above 200 mg/dL (5.2 mmol/L).

In patients whose primary dyslipidemia is markedly elevated triglycerides, the fibric acid derivatives gemfibrozil, bezafibrate, and fenofibrate have been effective in lowering triglyceride concentrations in preliminary studies (Table 3).[74,80] Gemfibrozil reduced triglycerides 83 and 60% in two separate studies of 6 and 25 patients, respectively. Miller and co-workers conducted a 16-week, randomized, double blind comparative study of low-saturated-fat diet alone versus low-saturated-fat diet plus gemfibrozil in patients with triglycerides > 265 mg/dL (3 mmol/L).[85] Gemfibrozil reduced triglycerides by 117 mg/dL (1.326 mmol/L) compared to an increase of 33 mg/dL (0.37 mmol/L) ($P = .06$) with dietary intervention alone. In a separate investigation, bezafibrate lowered triglycerides by 68% in 13 hyperlipidemic patients on protease inhibitors.[80] Fenofibrate reduced triglyceride concentrations from 1450 (16.4 mmol/L) to 337 mg/dL (3.8 mmol/L) (-77%) and from 1985 (22.4 mmol/L) to 322 mg/dL (3.6 mmol/L) (-84%) in two HIV positive protease inhibitor recipients after 10 months of treatment.[83] A second investigation with fenofibrate noted a mean reduction in triglycerides from 988 (11.2 mmol/L) to 263 mg/dL (3.0 mmol/L) (-73%) in 9 protease inhibitor recipients.[84] Cholesterol was reduced from 250 (6.5 mmol/L) to 227 mg/dL (5.9 mmol/L) (-9%) in this cohort. Because mean baseline triglyceride concentrations ranged from 988-1985 mg/dL (11.2 – 22.4 mmol/L) in these reports, the acute risk of pancreatitis may have been lowered in these patients. However, mean triglyceride concentrations still remained elevated (417-573 mg/dL [4.7 -6.5 mmol/L]) after treatment.

Although not indicated for the treatment of hyperlipidemia per se, metformin and the glitazones (rosiglitazone and pioglitazone) may stabilize or even improve triglyceride levels in HIV-infected patients with insulin resistance. Indeed, Hadigan et al. observed a 4 mg/dL (0.045 mmol/L) mean increase in triglycerides among 14 non-diabetic HIV-infected patients with fat redistribution treated with metformin 500 mg twice daily for 3 months.[86] In the same study, 11 patients who received placebo experienced a 121 mg/dL (1.37 mmol/L) mean increase in triglycerides over the same time period.[86] The glitazones (rosiglitazone and pioglitazone) either alone or in combination with metformin may also positively affect triglyceride levels.[30] ACTG 5082, a study designed to investigate metformin and rosiglitazone (alone and in combination) for the treatment of HIV-infected patients with lipodystrophy and hyperinsulinemia, is currently underway.

Switching Protease Inhibitor Therapy

Antihyperlipidemic therapy frequently fails to return cholesterol and triglyceride concentrations to normal. As such, coronary risks likely persist in a number of individuals with protease inhibitor-related hyperlipidemia. To this end, discontinuing protease inhibitor therapy and replacing the offending agent with another less lipogenic medication may be beneficial in a number of patients. The medications most commonly chosen to replace protease inhibitors in hopes of improving lipid profiles are the NNRTIs efavirenz and nevirapine, and the NRTI abacavir.

Efavirenz. Efavirenz is now recognized as the most potent NNRTI available, and regimens containing the drug are comparable and perhaps superior in efficacy to those containing protease inhibitors.[87,88] By this rationale, switching protease inhibitor-containing regimens for those containing efavirenz, may improve lipid profiles in patients without compromising antiviral efficacy.

At least 4 prospective studies, that report baseline and follow-up total cholesterol concentrations, have been conducted to evaluate the influence of efavirenz on serum lipid levels in patients previously receiving protease inhibitors.[89-92] The number of patients in these studies ranged from 20 to 61 and baseline total cholesterol averaged 252 mg/dL (6.5 mmol/L) (213-262 [5.5 -6.8 mmol/L]). After 7 months follow-up, total cholesterol concentrations were essentially unchanged at 241 mg/dL (6.2 mmol/L). In one study with a control arm, total cholesterol changed from 204 to 211 mg/dL (5.3 to 5.5 mmol/L) among patients who remained on protease inhibitor therapy.[91] Conversely, triglyceride concentrations declined from 708 to 378 mg/dL (8 – 4.3 mmol/L; $P < .01$), 305 to 262 mg/dL (3.4 – 3.0 mmol/L; P = NS), 209 to 144 mg/dL (2.4 – 1.6 mmol/L; $P < .03$), and 178 to 157 mg/dL (2.0 – 1.8 mmol/L) among 4 prospective investigations where efavirenz was used to replace protease inhibitor therapy.[89-91,93] In a study with a control arm (continued protease inhibitor therapy) , triglycerides changed from 207 to 212 mg/dL (2.3 to 2.4 mmol/L).[91] Moyle et al. recently reported increases of 15.6 and 57.5% in cholesterol and triglyceride concentrations, respectively, in 23 patients 1 year after switching to efavirenz from a protease

Table 3. Pharmacologic Treatment of Hyperlipidemia Associated with Protease Inhibitor Use in Patients with Hyperlipidemia

Antihyperlipidemic intervention	n	Baseline serum lipoprotein levels [a,b,c]	Serum lipoprotein levels post treatment[d]	Duration of treatment (follow-up)	Reference
gemfibrozil 600 mg twice daily; retrospective chart review	6	CH: Not reported TG: 1803 (716-2847)	CH: 200-230 ("no change") TG: 417 (range NR)	5 months ± 1 month median follow up	74
pravastatin 40 mg daily + dietary advice (n=15) versus dietary advice alone (n=16); prospective, randomized, open label	31	*Dietary Advice* CH: 286 (263-305; n=16) TG: 359 (195-528; n=16) LDL: 181 (150-211; n=10) HDL: 34 (28-39; n=16) *Pravastatin + Dietary Advice* CH: 290 (259-320; n=15) TG: 350 (251-577; n=15) LDL: 180 (158-201; n=11) HDL: 36 (31-42; n=15)	*Dietary Advice* CH: 274 (255-290; n=12; *P* > .05) TG: 316 (203-372; n=12) LDL: 178 (163-193; n=12) HDL: 36 (31-42; n=12) *Pravastatin + Dietary Advice* CH: 243 (212-274; n=14; *P*< .05) TG: 323 (188-492; n=14) LDL: 133 (106-160; n=11) HDL: 39 (35-42; n=14)	6 months	15
pravastatin 20 mg daily; prospective, open label	19	CH: 313 (178-398) TG: 813 (206-1857)	CH: 254 (185-291); *P*< .01 TG: 512 (211-772); *P*< .01	2 months	79
bezafibrate 400 mg daily; prospective	13	CH: 376 ± 154 TG: 1800 ± 2335	CH: 382 ± 97 TG: 573 ± 38	3 months	80
pravastatin 20 mg daily for 12 weeks; dose π'ed to 40 mg daily after 4 weeks if needed; prospective	17	LDL: 216 ± 44 (n=9) HDL: 41 ± 10 TG: 607 ± 625	LDL: 158 ± 14; *P* = .003 HDL: 43 ± 10; *P* = .36 TG: 526 ± 689; *P* = .22	3 months	14
pravastatin (n=5), lovastatin (n=13), simvastatin (n=10), atorvastatin (n=2); retrospective chart review	30	*pravastatin* CH: 315 TG: 478 *lovastatin* CH: 436 TG: 1230 *simvastatin* CH: 318 TG: 533 *atorvastatin* CH: 402 TG: 867	*pravastatin* CH: 249 TG: 436 *lovastatin* CH: 31 1 TG: 718 *simvastatin* CH: 233 TG: 380 *atorvastatin* CH: 258 TG: 466	4-10 months	70
gemfibrozil (n=25), atorvastatin (n=10), gemfibrozil + atorvastatin (n=19) and diet + exercise (n=20): NCEP Guidelines used and groups compared	74	*atorvastatin + gemfibrozil* CH: 297 TG: 982 *gemfibrozil* CH: 313 TG: 1354 *atorvastatin* CH: 270 TG: 274 *diet + exercise* CH: 243 TG: 336	*atorvastatin + gemfibrozil* CH: 220; *P* =.0004 TG: 425; *P* =.01 *gemfibrozil* CH: 220; *P* =.004, TG: 540; *P* =.01 *atorvastatin* CH: 220; *P* =.004, TG: 212; *P* = > .05 *diet + exercise* CH: 216; *P* = .03, TG: 265; *P* = .02	6 months	81
atorvastatin 10-20 mg daily	15	CH: 363 TG: 1000	CH: 247 TG: 680	15 months	82
fenofibrate 268 mg daily	2	CH: 268 TG: 1718	CH: 216 TG: 330	10 months	83
fenofibrate 201 mg daily	9	CH: 250 TG: 988	CH:227 TG:263; *P* < .05	3 months	84
gemfibrozil 600 mg twice daily + low-saturated-fat diet (n=16) compared to low-saturated-fat diet alone (n=20)	36	CH: 263 (all patients) TG: 496 (all patients)	CH: Not reported TG: 117 mg/dL reduction in gemfibrozil group; 33 mg/dL increase in diet group; *P* = .06)	3 months	85

[a]Mean or median values of the study population are reported

[b]CH: Total Cholesterol (mg/dL); TG: Triglycerides (mg/dL); NR: Not reported; numbers in parentheses represent ranges

[c]To convert mg/dL to mmol/L: multiply by 0.02586 for cholesterol and by 0.01129 for triglycerides

[d]*P* values are reported where available

inhibitor-containing regimen.[94] In general however, patients with elevated concentrations of cholesterol and triglycerides at baseline remained with elevated concentrations while patients with normal lipid levels at baseline remained normal.

Virologic suppression was maintained with efavirenz in all of the above investigations. Several other studies, that are retrospective in nature or do not report complete baseline and follow-up data, describe variable effects of switching to efavirenz on serum lipid concentrations.[95-97] Based on this limited data, select patients with primary hypertriglyceridemia may benefit from switching to efavirenz; total cholesterol concentrations however, do not improve in most patients. In most foreseeable circumstances, virologic control may be expected to be maintained when switching to efavirenz as long as patients are NNRTI naive and/or their virus does not express mutations that confer NNRTI resistance. Larger controlled studies that report lipoprotein subfractions and have extensive follow-up will further define the role of switching to efavirenz as a means of improving protease inhibitor-related hyperlipidemia.

Nevirapine. The NNRTI nevirapine has been evaluated in numerous pilot studies for its ability to improve hyperlipidemia associated with protease inhibitor use when it is exchanged for an offending protease inhibitor.[91,98-102] In general, most investigations report reductions in total cholesterol (-7 to –21%) and triglycerides (-0 to -44% [median change: -31%]) after switching protease inhibitor therapy for a nevirapine-containing regimen. Collectively, these results represent data from 305 patients (11 to 138 patients per investigation) followed over 3 to 7 months. The vast majority of patients in these nevirapine "switch" studies had viral loads < 50-500 copies/mL or were NNRTI naïve at the time of nevirapine initiation. While most patients in these studies maintained virologic suppression, Buisson et al. reported a 6.3% virologic failure rate (in 4/68 patients; defined as HIV-RNA > 50 copies/mL) within 6 months after switching to nevirapine.[103] All patients in this study had HIV-RNA < 50 copies/mL for 1 year prior to study participation. Similarly, Barriero and co-workers observed viral rebound (> 50 copies/mL) in 11% of patients over a 6-month period after exchanging protease inhibitor therapy for nevirapine.[100] These composite data suggest that switching from a protease inhibitor-containing regimen to one containing nevirapine may result in modest improvements in cholesterol and triglyceride concentrations. However, only patients who are sufficiently virologically suppressed (undetectable HIV-RNA) or NNRTI naïve should be routinely considered as candidates for switching to nevirapine; even then, patients must be closely monitored for changes in HIV-RNA and CD4+ counts. Genotypic or phenotypic resistance testing may be useful when deciding whether to switch patients to nevirapine for the management of protease inhibitor-associated hyperlipidemia.

Abacavir. Combination therapy with abacavir is now considered HAART.[104] Nonetheless, few studies have assessed the usefulness of exchanging protease inhibitor therapy for the NRTI abacavir among protease inhibitor recipients with hyperlipidemia. Clumeck et al. reported significant reductions in cholesterol and non-fasting triglyceride plasma levels at 48 weeks in patients switched to abacavir from a protease inhibitor.[104] On intent-to-treat analysis, patients switched to abacavir experienced reductions in triglycerides of 12 mg/dL (0.14 mmol/L; $P = .035$) and cholesterol of 20 mg/dL (0.51 mmol/L; $P < .001$). Of note, this study was designed to assess the virologic and immunologic efficacy of switching from a protease inhibitor-containing regimen to one containing abacavir. As such, only 47 and 61% of abacavir recipients had elevated triglycerides and total cholesterol at baseline; this likely explains, to some degree, the minimal decline in serum lipids with abacavir. Opravil et al. compared the influence of switching to abacavir (n=84) versus continuing protease inhibitor therapy (n=79) on non-fasted cholesterol, triglycerides, and HIV-RNA.[105] All patients had HIV-RNA < 50 copies/mL for ≥ 6 months prior to study participation and none possessed the 215 resistance mutation. Virologic failure was defined as two consecutive HIV-RNA measurements above 400 copies/mL. After a 1-year follow-up, abacavir was associated with reductions in non-fasting cholesterol (46 mg/dL [1.2 mmol/L]) and triglycerides (89 mg/dL [1.0 mmol/L]) compared to baseline (actual values not reported). However, there were 11/84 (13%) virologic failures in the abacavir arm compared to 5/79 (6%) in the protease inhibitor arm. Compared to patients who continued protease inhibitor therapy, a second study did not observe reductions in cholesterol or triglycerides among 16 patients switched from a protease inhibitor-containing regimen to abacavir.[106] Thus, it is unclear whether switching to abacavir provides a clinically significant improvement in hyperlipidemia secondary to protease inhibitor use. Perhaps of greater concern, is whether abacavir is potent enough to maintain virologic suppression when used to replace protease inhibitor therapy; particularly in NRTI experienced patients with HIV-RNA levels exceeding 100,000 copies/mL.[107] Therefore, before exchanging a protease inhibitor-containing regimen for one containing abacavir, a thorough NRTI history should be obtained that takes into full account potential cross-resistance between abacavir and other NRTIs. In addition, the use of genotypic or phenotypic resistance testing to guide therapy should also be strongly considered in this scenario.

Conclusion

The HIV protease inhibitors have been associated with a syndrome of abnormal fat redistribution, insulin resistance, and hyperlipidemia. This syndrome, superimposed upon lipid abnormalities associated with HIV infection itself, may predispose patients

to pathophysiologic events including premature atherosclerosis and pancreatitis. Treatment of hyperlipidemia should follow NCEP guidelines as closely as possible. Every effort should be made to modify CHD risk factors (i.e. smoking cessation, and control of hypertension and diabetes) and maximize lifestyle modifications — primarily dietary intervention and exercise — in patients with protease inhibitor-associated hyperlipidemia. Where indicated, treatment usually consists of either pravastatin or atorvastatin for patients with elevated LDL and/or total cholesterol. Atorvastatin is more potent (on a per milligram basis) in lowering cholesterol and triglyceride concentrations, but it is also associated with a greater number of drug interactions compared to pravastatin. Furthermore, pravastatin has proven beneficial in the primary prevention of myocardial infarction and death from cardiovascular causes; such data is absent for atorvastatin.[108] Simvastatin and lovastatin are not recommended for concurrent use with HIV protease inhibitors due to significant drug interactions. A fibric acid derivative (gemfibrozil or fenofibrate) should be used for patients with primary hypertriglyceridemia. In certain patients statins and fibrates may be used concurrently with careful monitoring for liver and skeletal muscle toxicity. Select patients may experience improvements in lipid concentrations by exchanging the offending protease inhibitor for efavirenz, nevirapine, or abacavir with or without concomitant lipid lowering agents.

References available upon request.

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

301-496-2407
Pager 301-285-4661
Building 10, Room 1S-259